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U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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Carcinogenesis Testing Program
Division of Cancer Cause and Prevention
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20014

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CONTRIBUTORS: This report presents the results of the bioassay of dieldrin for possible carcinogenicity, conducted for the Carcinogenesis Testing Program, Division of Cancer Cause and Prevention, National Cancer Institute (NCI), Bethesda, Maryland. The bioassay was conducted by Stanford Research Institute, Menlo Park, California, initially under direct contract to NCI and currently under a subcontract to Tracor Jitco, Inc., prime contractor for the NCI carcinogenesis bioassay program.

The experimental design and doses were determined by Drs. R. R. Bates[1,2], D. C. L. Jones[3], D. P. Sasmore[3], G. W. Newell[3], and R. M. Elashoff[4], and Mr. W. E. Davis[3]. The principal investigator was Dr. D. C. L. Jones; the technical supervisor of animal treatment, observation, and data handling was Mr. W. E. Davis; necropsy and tissue fixation were supervised by Dr. D. P. Sasmore.

Histopathologic examinations were performed by Dr. H. Elster[5], and the diagnoses included in this report represent his interpretation. Neoplasms and compound-related hyperplastic lesions were reviewed by Dr. W. M. Busey[6], who also prepared the interpretive pathology summary included in this report.

Animal pathology tables and survival tables were compiled at EG&G Mason Research Institute[7]. The statistical analyses were performed by Dr. J. R. Joiner[8], using methods selected for the bioassay program by Dr. J. J. Gart[9]. Chemicals used in this bioassay were analyzed at Stanford Research Institute and the analytical results were reviewed by Dr. S. S. Olin[8].

This report was prepared at Tracor Jitco under the direction of NCI. Those responsible for the report at Tracor Jitco were Dr. Marshall Steinberg[8], Director of the Bioassay Program; Drs. J. F. Robens[8] and C. H. Williams[8], toxicologists; Dr. R. L. Schueler[8], pathologist; Ms. L. A. Waitz[8] and Mr. W. D. Reichardt[8], bioscience writers; and Dr. E. W. Gunberg[8], technical editor, assisted by Ms. Y. E. Presley[8].

The statistical analysis was reviewed by members of the Mathematical Statistics and Applied Mathematics Section of NCI[9]: Dr. John J. Gart, Mr. Jun-mo Nam, Dr. Hugh M. Pettigrew, and Dr. Robert E. Tarone.

The following other scientists at the National Cancer Institute were responsible for evaluating the bioassay experiment, interpreting the results, and reporting the findings:

Dr. Kenneth C. Chu
Dr. Cipriano Cueto, Jr.
Dr. J. Fielding Douglas
Dr. Dawn G. Goodman
Dr. Richard A. Griesemer
Mr. Harry A. Milman
Dr. Thomas W. Orme
Dr. Robert A. Squire[10]
Dr. Jerrold M. Ward

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[1]Carcinogenesis Testing Program, Division of Cancer Cause and Prevention, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

[2]Now with the Office of the Commissioner, Food and Drug Administration, Rockville, Maryland.

[3]Stanford Research Institute, Menlo Park, California.

[4]Department of Biomathematics, Center for the Health Sciences, University of California, Los Angles, California.

[5]Department of Pathology, David M. Brotman Memorial Hospital, 3828 Hughes Avenue, Culver City, California.

[6]Experimental Pathology Laboratories, Inc., P.O. Box 474, Herndon, Virginia.

[7]EG&G Mason Research Institute, 1530 East Jefferson Street, Rockville, Maryland.

[8]Tracor Jitco, Inc., 1776 East Jefferson Street, Rockville, Maryland.

[9]Mathematical Statistics and Applied Mathematics Section, Biometry Branch, Field Studies and Statistics, Division of Cancer Cause and Prevention, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

[10]Now with the Division of Comparative Medicine, Johns Hopkins University, School of Medicine, Traylor Building, Baltimore, Maryland.

SUMMARY

A bioassay of purified technical-grade dieldrin for possible carcinogenicity was conducted by administering the test chemical in feed to Fischer 344 rats.

Groups of 24 rats of each sex were administered dieldrin at one of three doses, either 2, 10, or 50 ppm, for 104-105 weeks. Matched controls consisted of groups of 24 untreated rats of each sex. All surviving rats were killed at 104-105 weeks.

Body weights of the rats were essentially unaffected by the treatment, but typical signs of organochlorine intoxication including hyperexcitability, tremors, and coma were observed in high-dose males beginning in week 76 and in high-dose females beginning in week 80. Survival was not adversely affected, and adequate numbers of rats were available for meaningful statistical analyses of the incidences of tumors.

A variety of neoplasms occurred in control and treated rats; however, the incidences were not related to treatment.

It is concluded that under the conditions of this bioassay, dieldrin was not carcinogenic in Fischer 344 rats.

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I. INTRODUCTION

Dieldrin (CAS 60-57-1; NCI C00124) is a chlorinated cyclodiene pesticide. It is also a metabolic conversion product of aldrin, another pesticide, and can be expected to appear in the environment following the use of either chemical. Dieldrin was first introduced in the 1950's for use by cotton growers when the chemical was found to be more effective than aldrin, and later, was used as an insecticide for other crops, for public health pest control, and for mothproofing woolen goods (Federal Register, 1974).

Based partly on the evidence of the hepatocarcinogenicity of dieldrin in the mouse, the registration of all products containing dieldrin was cancelled in 1974 (Federal Register, 1974).

Dieldrin and aldrin were selected for testing in both rats and mice in the bioassay program in 1969, because data regarding their carcinogenicity were controversial and often inadequate, and because there was a potential for long-term human exposure to residues, particularly in foods. A report on the bioassays of both chemicals in both species has been published (National Cancer Institute, 1977). A second abbreviated study of dieldrin was conducted as a part of a larger study that was designed to

assess the combined effects of a group of known or suspected carcinogens. Only the results of this second study pertinent to dieldrin are reported herein.

II. MATERIAL AND METHODS

A. Chemicals

Technical-grade dieldrin was purchased from Shell Development Company, Modesto, California, in a single batch (Lot No. 8-JCD-32).

The chemical was purified before analysis and use in the bioassay. Purification was by treatment of a hot hexane solution with Norit and by filtration, recrystallization from hexane, and finally, recrystallization from absolute methanol.

The identity and purity of this product were confirmed by analyses at Stanford Research Institute. The melting point was 179-181°C (literature: 175-176°C), and the elemental analyses (C, H, Cl) were correct for $C_{12}H_8Cl_6O$, the molecular formula of dieldrin. The identity of the chemical was determined by nuclear magnetic resonance and infrared spectra, which were in agreement with the structure and matched the spectra given in the literature. No attempt was made to identify or quantitate impurities.

The chemical was stored at room temperature in capped plastic bottles.

B. Dietary Preparation

All diets were formulated every 2 weeks using Low Fat Lab Chow®

(Ralston Purina Co., St. Louis, Mo.). A stock diet containing 250 ppm dieldrin was prepared by first grinding the dieldrin to a fine powder and then mixing by hand a weighed amount with a small amount of feed. Corn oil and more feed were then added to give a final concentration of 250 ppm dieldrin and 3% corn oil, and final mixing was accomplished with a Hobart blender. Each stock diet was analyzed for content of dieldrin by a method involving extraction, Florisil® chromatography, and quantitation by gas-liquid chromatography. Concentrations of 250 ppm $\pm$ 25 ppm were considered acceptable for use in preparing test diets. Dieldrin at 250 ppm in the stock diet was found to be stable when held in rat feeders at room temperature for a 2-week period.

To obtain test diets having appropriate concentrations of dieldrin, the stock diet was diluted, as required, with control diet containing 3% corn oil and mixed in a Hobart blender. Stock and test diets were stored at room temperature in covered plastic containers.

C. Animals

Male and female Fischer 344 rats, obtained through contracts of the Division of Cancer Treatment, National Cancer Institute, were used in these bioassays. The rats were obtained from Simonsen Laboratory, Gilroy, California. On arrival at the laboratory,

all animals were quarantined for 2 weeks as an acclimation period. Following this period, all males gaining less than 25 grams, all females gaining less than 15 grams, and all unhealthy animals were culled. The remaining animals were assigned to cages, one per cage, until each cage contained three animals. Cages were then numbered and assigned to control and treated groups using a computer-generated randomization table. Rats were ear-clipped for individual identification.

D. Animal Maintenance

All animals were housed in temperature- and humidity-controlled rooms. The temperature was maintained at 22°C with a range of 21-24°C, and the relative humidity was maintained at approximately 45%. The room air was changed 10 times per hour and was maintained under positive pressure to the access halls. Fluorescent lighting provided illumination 12 hours per day. Food and water were available ad libitum. Drinking water was softened, filtered, sterilized with ultraviolet light, and supplied by means of an automatic watering system.

The rats were housed three per cage in polycarbonate cages equipped with disposable polyester woven filter tops. Autoclaved hardwood chips (Iso-Dri®, Becton, Dickinson, and Carworth, Warrensburg, N. Y.) were used as bedding. The cages were

changed, washed, and provided with fresh bedding twice per week. Filter tops were replaced once per month.

Rats fed dieldrin were housed in the same room as rats treated with hexachlorophene (CAS 70-30-4), aflatoxin B_1 (CAS 1162-65-8), Aroclor® 1254 (CAS 27323-18-8), or lead (II) acetate (CAS 301-04-2).

E. Subchronic Studies

Subchronic feeding studies were conducted with male and female Fischer 344 rats to estimate the maximum tolerated dose of dieldrin, on the basis of which low, mid, and high concentrations (hereinafter referred to as "low doses", "mid doses", and "high doses") were determined for administration in the chronic studies. In the subchronic studies, dieldrin was added to feed in concentrations of 25, 50, 100, 200, or 300 ppm. Treated and control groups each consisted of 15 male and 15 female rats. The chemical was provided in the feed to the treated groups for 8 weeks.

All rats fed at 200 or 300 ppm dieldrin died within 2 weeks. At 100 ppm, during the first week, body weights of females were less than those of controls, while those of males appeared comparable to those of controls. Neuronal necrosis of the brain was noted on histologic examination of those animals receiving 100 ppm, but

not 50 ppm, dieldrin. The low, mid, and high doses for the chronic studies were set at 2, 10, and 50 ppm.

F. Design of Chronic Studies

The design of the chronic studies is shown in table 1.

G. Clinical and Pathologic Examinations

All animals were observed twice daily for signs of toxicity and palpated for masses at each weighing. Animals were weighed individually every other week for 12 weeks, and every fourth week for the remainder of the study. Animals that were moribund at the time of clinical examination were killed and necropsied.

The pathologic evaluation consisted of gross examination of major tissues, major organs, and all gross lesions from killed animals and from animals found dead. The following tissues were routinely examined microscopically from both control and treated animals: brain, liver, kidney, lung, pituitary, spleen, and testis. In addition, sections of stomach, thyroid, trachea, urinary bladder, and uterus were examined from a majority of the control animals; these tissues were examined from treated animals only if a lesion was found at necropsy. Gross lesions from any other tissues in all animals were also examined microscopically. The different tissues were preserved in 10% buffered formalin,

Table 1. Design of Dieldrin Chronic Feeding Studies in Rats

Sex and Treatment Group	Initial No. of Animals[a]	Dieldrin in Diet[b] (ppm)	Time on Study	
			Treated (weeks)	Untreated (weeks)
Male				
Matched-Control	24	0		105
Low-Dose	24	2	104	
Mid-Dose	24	10	105	
High-Dose	24	50	105	
Female				
Matched-Control	24	0		105
Low-Dose	24	2	104	
Mid-Dose	24	10	105	
High-Dose	24	50	105	

[a]All animals were 53 ± 2 days of age when placed on study.

[b]All diets contained 3% corn oil.

embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Special staining techniques were utilized when indicated for more definitive diagnosis.

A few of the tissues selected by design from some animals were not examined, particularly from those animals that died early. Also, one animal was missing. Thus, the number of animals from which particular organs or tissues were examined microscopically varies, and does not necessarily represent the number of animals that were placed on study in each group.

H. Data Recording and Statistical Analyses

Pertinent data on this experiment have been recorded in an automatic data processing system, the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, clinical observations, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969). Data tables were generated for verification of data transcription and for statistical review.

These data were analyzed using the statistical techniques described in this section. Those analyses of the experimental results that bear on the possibility of carcinogenicity are discussed in the statistical narrative sections.

Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958) and are presented in this report in the form of graphs. Animals were statistically censored as of the time that they died of other than natural causes or were found to be missing; animals dying from natural causes were not statistically censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) extensions of Cox's methods for testing for a dose-related trend. One-tailed P values have been reported for all tests except the departure from linearity test, which is only reported when its two-tailed P value is less than 0.05.

The incidence of neoplastic or nonneoplastic lesions has been given as the ratio of the number of animals bearing such lesions at a specific anatomic site (numerator) to the number of animals necropsied (denominator).

The purpose of the statistical analyses of tumor incidence is to determine whether animals receiving the test chemical developed a significantly higher proportion of tumors than did the control animals. As a part of these analyses, the one-tailed Fisher exact test (Cox, 1970) was used to compare the tumor incidence of a control group with that of a group of treated animals at each dose level. When results for a number of treated groups (k) are

compared simultaneously with those for a control group, a correction to ensure an overall significance level of 0.05 may be made. The Bonferroni inequality (Miller, 1966) requires that the P value for any comparison be less than or equal to 0.05/k. In cases where this correction was used, it is discussed in the narrative section. It is not, however, presented in the tables, where the Fisher exact P values are shown.

The Cochran-Armitage test for linear trend in proportions, with continuity correction (Armitage, 1971), was also used. Under the assumption of a linear trend, this test determines if the slope of the dose-response curve is different from zero at the one-tailed 0.05 level of significance. Unless otherwise noted, the direction of the significant trend is a positive dose relationship. This method also provides a two-tailed test of departure from linear trend.

A time-adjusted analysis was applied when numerous early deaths resulted from causes that were not associated with the formation of tumors. In this analysis, deaths that occurred before the first tumor was observed were excluded by basing the statistical tests on animals that survived at least 52 weeks, unless a tumor was found at the anatomic site of interest before week 52. When such an early tumor was found, comparisons were based exclusively on animals that survived at least as long as the animal in which

the first tumor was found. Once this reduced set of data was obtained, the standard procedures for analyses of the incidence of tumors (Fisher exact tests, Cochran-Armitage tests, etc.) were followed.

When appropriate, life-table methods were used to analyze the incidence of tumors. Curves of the proportions surviving without an observed tumor were computed as in Saffiotti et al. (1972). The week during which an animal died naturally or was sacrificed was entered as the time point of tumor observation. Cox's methods of comparing these curves were used for two groups; Tarone's extension to testing for linear trend was used for three groups. The statistical tests for the incidence of tumors which used life-table methods were one-tailed and, unless otherwise noted, in the direction of a positive dose relationship. Significant departures from linearity ($P < 0.05$, two-tailed test) were also noted.

The approximate 95 percent confidence interval for the relative risk of each treated group compared to its control was calculated from the exact interval on the odds ratio (Gart, 1971). The relative risk is defined as p_t/p_c where p_t is the true binomial probability of the incidence of a specific type of tumor in a treated group of animals and p_c is the true probability of the spontaneous incidence of the same type of tumor in a control

group. The hypothesis of equality between the true proportion of a specific tumor in a treated group and the proportion in a control group corresponds to a relative risk of unity. Values in excess of unity represent the condition of a larger proportion in the treated group than in the control.

The lower and upper limits of the confidence interval of the relative risk have been included in the tables of statistical analyses. The interpretation of the limits is that in approximately 95% of a large number of identical experiments, the true ratio of the risk in a treated group of animals to that in a control group would be within the interval calculated from the experiment. When the lower limit of the confidence interval is greater than one, it can be inferred that a statistically significant result ($P < 0.025$ one-tailed test when the control incidence is not zero, $P < 0.050$ when the control incidence is zero) has occurred. When the lower limit is less than unity, but the upper limit is greater than unity, the lower limit indicates the absence of a significant result while the upper limit indicates that there is a theoretical possibility of the induction of tumors by the test chemical, which could not be detected under the conditions of this test.

III. RESULTS

A. Body Weights and Clinical Signs

Mean body weights were essentially unaffected by the doses of dieldrin used in this bioassay (figure 1). Fluctuations in the growth curve may be due to mortality; as the size of the group diminishes, the mean body weight may be subject to wide variation. At week 40, an intercurrent infection caused respiratory problems and weight loss, but few animals died. No treatment for infection was given, and the animals recovered by the next scheduled weighing period.

At week 76, clinical signs of central nervous system disorders such as convulsions, muscle tremors, and nervous behavior were first noted in high-dose males, and around week 80, these signs were apparent in the high-dose females.

B. Survival

The Kaplan and Meier curves estimating the probabilities of survival for male and female rats fed dieldrin at the doses of this study, together with those of the controls, are shown in figure 2.

In neither sex is the Tarone test result significant at the 0.05 level for positive dose-related trend in mortality over the

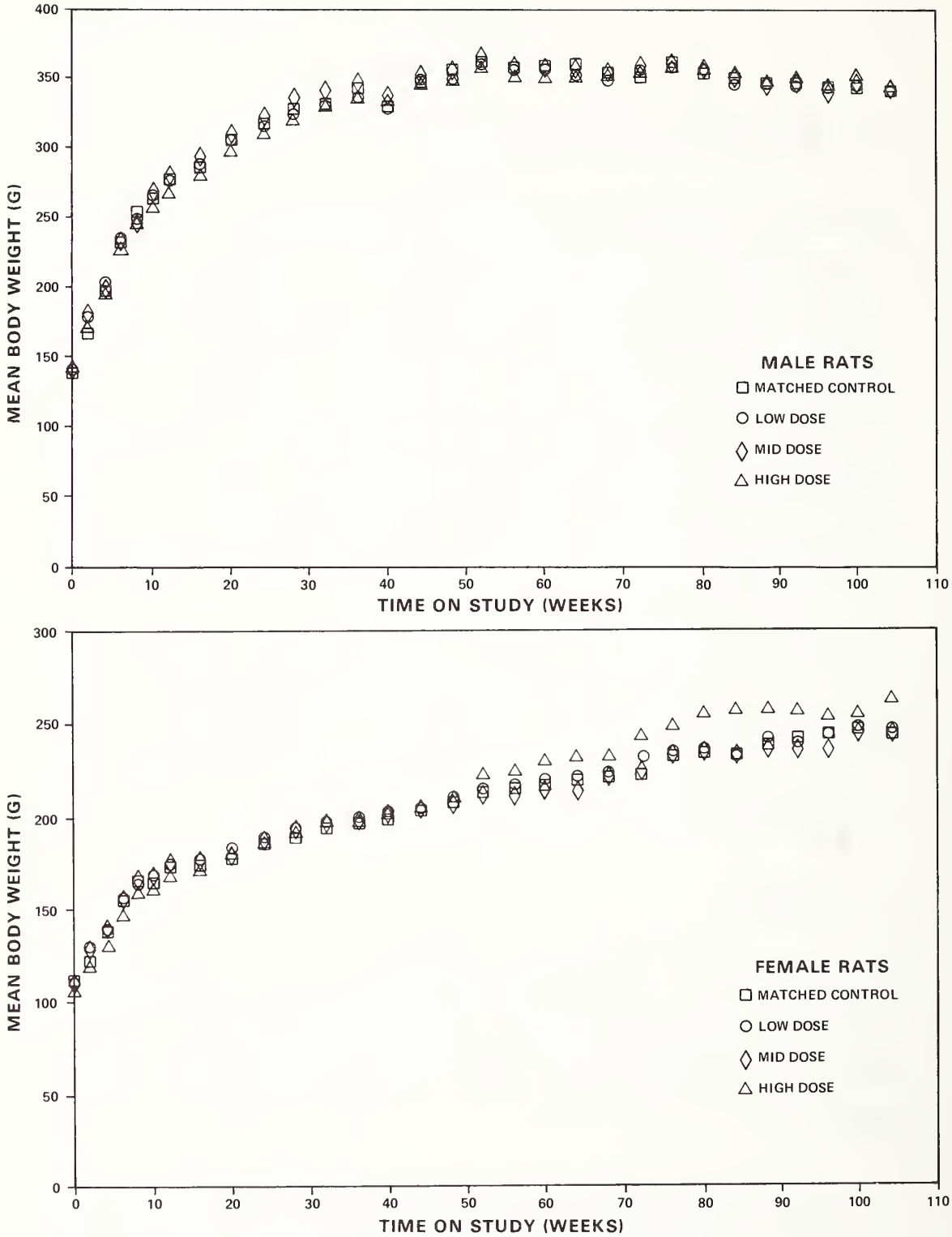

Figure 1. Growth Curves for Rats Fed Dieldrin in the Diet

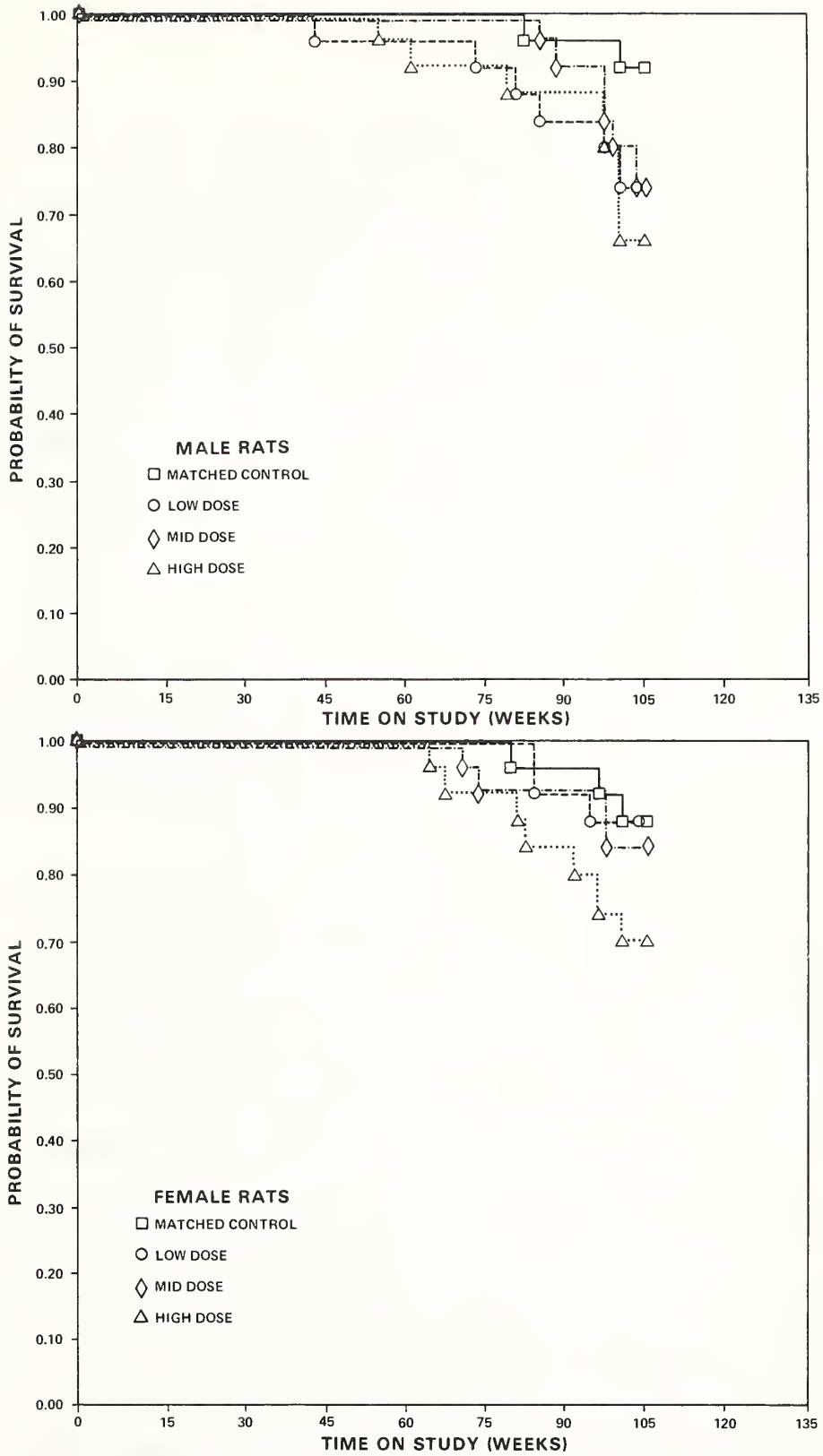

Figure 2. Survival Curves for Rats Fed Dieldrin in the Diet

period. In male rats, 67% of the high-dose group, 75% of the low- and mid-dose groups, and 92% of the matched-control group lived to the end of the study. In females, 70% of the high-dose group, 83% of the mid-dose group, and 88% of the low-dose and matched-control groups survived to termination of the study. Sufficient numbers of rats of both sexes were available for meaningful statistical analyses of the incidences of late-developing tumors.

C. Pathology

Histopathologic findings on neoplasms in rats are summarized in Appendix A, tables A1 and A2; findings on nonneoplastic lesions are summarized in Appendix B, tables B1 and B2.

A variety of neoplasms were observed in both the control and treated rats. The incidence of these neoplasms was comparable among the control and treated animals. Interstitial-cell tumors of the testes were the most frequently encountered neoplasms in the control and treated males. The next most commonly seen neoplasm was leukemia of either the lymphocytic or granulocytic type, and it generally involved multiple organs. Here again, the incidence of this neoplastic process was comparable among the control and treated male rats.

The following neoplasms occurred randomly throughout the control

and treated male and female rats: pituitary adenomas, thyroid adenomas, mammary gland adenomas and/or fibroadenomas, mesotheliomas involving the body cavities, and uterine endometrial stromal polyps.

The results of the histopathologic examination indicate that the administration of dieldrin at the three doses used in this study did not have a carcinogenic effect in the Fischer 344 rat. With the exception of interstitial-cell tumors of the testes, a relatively low incidence of neoplasia was seen in both the control and treated animals. A variety of incidental neoplastic processes were seen in both the control and treated rats at an incidence that would be expected in this strain of rat.

D. Statistical Analyses of Results

Tables C1 and C2 in Appendix C contain the statistical analyses of the incidences of those specific primary tumors that were observed in at least 5% of one or more treated groups of either sex. Due to the nature of the pathology protocol, the number of animals necropsied was used as the denominator.

In male rats, none of the incidences of tumors at any specific site are statistically significant. In female rats, although the Cochran-Armitage test result for positive dose-related trend in the proportions of endometrial stromal sarcoma of the uterus is

significant (P = 0.039), this positive finding cannot be established by the Fisher exact test. Since the Cochran-Armitage test is made to detect a linear trend, and in this instance only one incidence (high-dose 2/23 [9%]) is not zero, it is questionable whether a dose-associated trend has been found. When the incidences of stromal polyp and stromal sarcoma are combined, the results indicate a significant difference in the negative direction, due to the large incidence (13/24 [54%]) in the control group. The combined incidence of these two tumors in the four control groups available from this laboratory is 22/95 (23%), of which 13 diagnoses are from this study. There is no other specific incidence of tumors in female rats that is statistically significant. Significant results in the negative direction are also observed in the incidence of interstial-cell tumor of the testis and the incidence of endometrial stromal polyp of the uterus.

In some of the 95% confidence intervals for relative risk, shown in the tables, the value of one is included. This indicates the absence of positive significant results. It should also be noted that some of the intervals have an upper limit greater than one, indicating the theoretical possibility of the induction of tumors by dieldrin, which could not be detected under the conditions of this test.

IV. DISCUSSION

In this bioassay, dieldrin did not adversely affect the body weights of the treated rats, but typical signs of systemic organochlorine intoxication were observed at the high dose from approximately week 76 in males and week 80 in females. Survival was not adversely affected, and adequate numbers of rats were available for meaningful statistical analyses of the incidences of tumors.

A variety of neoplasms were found in both control and treated rats, none of which could be attributed to dieldrin. In this study, the predominant tumors were interstitial-cell tumors of the testes, which occurred in almost all the males in the control and treated groups, and granulocytic leukemia, which occurred at a low incidence in the control and treated groups of both sexes. Females in each of the control and treated groups also developed endometrial stromal polyps. Statistically, the incidences of these tumors were not significant, and the tumors were considered to be of spontaneous origin.

In another bioassay of dieldrin (National Cancer Institute, 1977), conducted with Osborne-Mendel rats and using time-weighted average doses of 29 and 59 ppm, the predominant tumors occurred in the pituitary and thyroid glands, but were not clearly related

to the administration of dieldrin. These tumors were not seen in the Fischer 344 rats in the present study, using a high dose of 50 ppm. However, the thyroids of the Fischer 344 rats treated with dieldrin were not routinely examined microscopically.

This bioassay is in agreement with previously published studies by Fitzhugh et al. (1964) and by Deichmann et al. (1970) using Osborne-Mendel rats, and by Walker et al. (1969) using Carworth Farm "E" strain rats, in which there were no significant increases in tumors among treated rats.

It is concluded that under the conditions of this bioassay, dieldrin was not carcinogenic in Fischer 344 rats.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS FED DIELDRIN IN THE DIET

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS FED DIELDRIN IN THE DIET

	CONTROL DOSE	LOW DOSE	MEDIUM DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	24	24	24	24
ANIMALS NECROPSIED	24	24	24	24
ANIMALS EXAMINED HISTOPATHOLOGICALLY	24	24	24	24
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(24)	(24)	(24)	(24)
ANGICSARCOMA				1 (4%)
OSTEOSARCOMA	1 (4%)			
RESPIRATORY SYSTEM				
#LUNG	(24)	(24)	(23)	(22)
CARCINOMA, NOS, METASTATIC				1 (5%)
OSTEOSARCOMA, METASTATIC	1 (4%)			
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(24)	(24)	(24)	(24)
LYMPHOCYTIC LEUKEMIA	1 (4%)			
GRANULOCYTIC LEUKEMIA	1 (4%)	5 (21%)	5 (21%)	5 (21%)
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
NONE				
URINARY SYSTEM				
#KIDNEY/CORTEX	(24)	(24)	(23)	(23)
CARCINOMA,NOS				1 (4%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL DOSE	LOW DOSE	MEDIUM DOSE	HIGH DOSE
#URINARY BLADDER	(15)	(1)		(1)
PAPILLOMA, NOS	1 (7%)			
ENDOCRINE SYSTEM				
#PITUITARY	(24)	(24)	(24)	(23)
ADENOMA, NOS		3 (13%)	1 (4%)	1 (4%)
#THYROID	(15)			(1)
SMALL-CELL CARCINOMA				1 (100%)
ADENOMA, NOS	1 (7%)			
#PANCREATIC ISLETS	(12)	(6)		(1)
ISLET-CELL CARCINOMA		1 (17%)		
REPRODUCTIVE SYSTEM				
#TESTIS	(24)	(24)	(24)	(24)
INTERSTITIAL-CELL TUMOR	24 (100%)	23 (96%)	24 (100%)	20 (83%)
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*TUNICA VAGINALIS	(24)	(24)	(24)	(24)
MESOTHELIOMA, NOS			1 (4%)	
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(24)	(24)	(24)	(24)
MESOTHELIOMA, MALIGNANT			1 (4%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL DOSE	LOW DOSE	MEDIUM DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	24	24	24	24
NATURAL DEATH@		2	1	6
MORIBUND SACRIFICE	2	4	5	2
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	22	18	18	16
ANIMAL MISSING				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	24	23	24	23
TOTAL PRIMARY TUMORS	29	32	32	29
TOTAL ANIMALS WITH BENIGN TUMORS	24	23	24	20
TOTAL BENIGN TUMORS	26	26	25	21
TOTAL ANIMALS WITH MALIGNANT TUMORS	3	6	6	8
TOTAL MALIGNANT TUMORS	3	6	6	8
TOTAL ANIMALS WITH SECONDARY TUMORS#	1			1
TOTAL SECONDARY TUMORS	1			1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			1	
TOTAL UNCERTAIN TUMORS			1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

@ INCLUDES AUTOLYZED ANIMALS

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS

SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE A2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS FED DIELDRIN IN THE DIET

	CONTROL DOSE	LOW DOSE	MEDIUM DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	24	24	24	24
ANIMALS MISSING				1
ANIMALS NECROPSIED	24	24	24	23
ANIMALS EXAMINED HISTOPATHOLOGICALLY	24	24	24	23
INTEGUMENTARY SYSTEM				
*SKIN	(24)	(24)	(24)	(23)
SQUAMOUS CELL CARCINOMA			1 (4%)	
*SUBCUT TISSUE	(24)	(24)	(24)	(23)
SQUAMOUS CELL CARCINOMA		1 (4%)		1 (4%)
RESPIRATORY SYSTEM				
#LUNG	(23)	(24)	(24)	(23)
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (4%)		
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(24)	(24)	(24)	(23)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (4%)			
GRANULOCYTIC LEUKEMIA	1 (4%)	3 (13%)	5 (21%)	4 (17%)
#LIVER	(24)	(24)	(24)	(23)
GRANULOCYTIC LEUKEMIA				1 (4%)
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
NONE				
URINARY SYSTEM				
*GENITOURINARY TRACT	(24)	(24)	(24)	(23)
PAPILLOMA, NOS			1 (4%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL DOSE	LOW DOSE	MEDIUM DOSE	HIGH DOSE
#URINARY BLADDER	(14)			
TRANSITIONAL-CELL CARCINOMA	1 (7%)			
ENDOCRINE SYSTEM				
#PITUITARY	(24)	(23)	(24)	(23)
ADENOMA, NOS	2 (8%)	7 (30%)	4 (17%)	2 (9%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(24)	(24)	(24)	(23)
ADENOMA, NOS		2 (8%)		
ADENOCARCINOMA, NOS		1 (4%)	1 (4%)	
CYSTADENOMA, NOS	1 (4%)			
FIBROMA	1 (4%)			
FIBROADENOMA	2 (8%)			2 (9%)
#UTERUS	(22)	(10)	(8)	(13)
ADENOCARCINOMA, NOS			1 (13%)	
LEIOMYOMA		1 (10%)		
ENDOMETRIAL STROMAL POLYP	13 (59%)	7 (70%)	4 (50%)	4 (31%)
ENDOMETRIAL STROMAL SARCOMA				2 (15%)
NERVOUS SYSTEM				
#BRAIN	(24)	(24)	(23)	(23)
HEMANGIOSARCOMA			1 (4%)	
OLIGODENDROGLIOMA	1 (4%)			
MENINGIOMA			1 (4%)	
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL DOSE	LOW DOSE	MEDIUM DOSE	HIGH DOSE
ALL OTHER SYSTEMS				
NONE				
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	24	24	24	24
NATURAL DEATH@	1		3	
MORIBUND SACRIFICE	2	3	1	7
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	21	21	20	16
ANIMAL MISSING				1
@ INCLUDES AUTOLYZED ANIMALS				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	17	17	16	14
TOTAL PRIMARY TUMORS	23	23	19	16
TOTAL ANIMALS WITH BENIGN TUMORS	14	13	9	8
TOTAL BENIGN TUMORS	19	18	9	8
TOTAL ANIMALS WITH MALIGNANT TUMORS	4	5	9	7
TOTAL MALIGNANT TUMORS	4	5	10	8
TOTAL ANIMALS WITH SECONDARY TUMORS#				
TOTAL SECONDARY TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT				
TOTAL UNCERTAIN TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
\# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

APPENDIX B

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS

IN RATS FED DIELDRIN IN THE DIET

TABLE B1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS FED DIELDRIN IN THE DIET

	CONTROL DOSE	LOW DOSE	MEDIUM DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	24	24	24	24
ANIMALS NECROPSIED	24	24	24	24
ANIMALS EXAMINED HISTOPATHOLOGICALLY	24	24	24	24
INTEGUMENTARY SYSTEM				
*SKIN	(24)	(24)	(24)	(24)
CYST, NOS			1 (4%)	
*SUBCUT TISSUE	(24)	(24)	(24)	(24)
EPIDERMAL INCLUSION CYST				1 (4%)
RESPIRATORY SYSTEM				
#TRACHEA	(15)			
INFLAMMATION, NOS	2 (13%)			
INFLAMMATION, ACUTE	1 (7%)			
#LUNG/BRONCHUS	(24)	(24)	(23)	(22)
BRONCHIECTASIS	1 (4%)	1 (4%)		2 (9%)
INFLAMMATION, NOS		1 (4%)	1 (4%)	
#LUNG	(24)	(24)	(23)	(22)
ATELECTASIS		5 (21%)	1 (4%)	2 (9%)
CONGESTION, NOS	14 (58%)	16 (67%)	11 (48%)	8 (36%)
HEMORRHAGE			1 (4%)	
INFLAMMATION, NOS		1 (4%)		
INFLAMMATION, FOCAL	1 (4%)			
ABSCESS, NOS	2 (8%)	2 (8%)	2 (9%)	2 (9%)
HEMATOPOIETIC SYSTEM				
#SPLEEN	(23)	(24)	(24)	(23)
CONGESTION, NOS	1 (4%)			
FIBROCALCIFIC NODULE				1 (4%)
INFARCT, NOS		1 (4%)		
#LYMPH NODE	(6)	(3)		(3)
LYMPHANGIECTASIS		1 (33%)		3 (100%)

\# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL DOSE	LOW DOSE	MEDIUM DOSE	HIGH DOSE
CONGESTION, NOS		1 (33%)		
INFLAMMATION, GRANULOMATOUS		1 (33%)		
REACTION, FOREIGN BODY	1 (17%)			
HISTIOCYTOSIS	2 (33%)			
#RENAL LYMPH NODE	(6)	(3)		(3)
LYMPHANGIECTASIS	1 (17%)			
CIRCULATORY SYSTEM				
#HEART				(1)
HEMORRHAGE				1 (100%)
INFLAMMATION, NOS				1 (100%)
#HEART/ATRIUM				(1)
DEGENERATION, NOS				1 (100%)
DIGESTIVE SYSTEM				
#LIVER	(24)	(23)	(23)	(23)
CONGESTION, NOS	12 (50%)	6 (26%)	3 (13%)	8 (35%)
SCAR	1 (4%)			
HYPERPLASIA, NODULAR	2 (8%)			4 (17%)
ANGIECTASIS			1 (4%)	1 (4%)
#LIVER/CENTRILOBULAR	(24)	(23)	(23)	(23)
CONGESTION, NOS				1 (4%)
#STOMACH	(23)	(4)		(3)
DIVERTICULUM	1 (4%)			
EPIDERMAL INCLUSION CYST	1 (4%)			
CONGESTION, NOS		1 (25%)		
DIVERTICULITIS	1 (4%)			
#CECUM	(3)	(1)		(2)
CONGESTION, NOS		1 (100%)		
NECROSIS, NOS				1 (50%)
HYPERPLASIA, LYMPHOID		1 (100%)		
*ANUS	(24)	(24)	(24)	(24)
DIVERTICULUM				1 (4%)
DIVERTICULITIS				1 (4%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL DOSE	LOW DOSE	MEDIUM DOSE	HIGH DOSE
URINARY SYSTEM				
#KIDNEY	(24)	(24)	(23)	(23)
CALCULUS, NOS		1 (4%)		
HYDRONEPHROSIS		1 (4%)		
CYST, NOS				2 (9%)
PYELONEPHRITIS, NOS	1 (4%)		1 (4%)	2 (9%)
PYELONEPHRITIS, FOCAL				1 (4%)
#URINARY BLADDER	(15)	(1)		(1)
CONGESTION, NOS		1 (100%)		
INFLAMMATION, ACUTE				1 (100%)
ENDOCRINE SYSTEM				
#PITUITARY	(24)	(24)	(24)	(23)
CONGESTION, NOS		1 (4%)		1 (4%)
#ADRENAL				(1)
CONGESTION, NOS				1 (100%)
#THYROID	(15)			(1)
INFLAMMATION, NOS	1 (7%)			
NODULE	1 (7%)			
REPRODUCTIVE SYSTEM				
*SEMINAL VESICLE	(24)	(24)	(24)	(24)
DILATATION, NOS		2 (8%)		
HYPERPLASIA, FOCAL			1 (4%)	
#TESTIS	(24)	(24)	(24)	(24)
ATROPHY, NOS		1 (4%)		1 (4%)
NERVOUS SYSTEM				
#BRAIN	(24)	(23)	(24)	(24)
CONGESTION, NOS		1 (4%)	1 (4%)	
HEMORRHAGE	1 (4%)			
CALCIFICATION, FOCAL		1 (4%)		
SPECIAL SENSE ORGANS				
NONE				

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL DOSE	LOW DOSE	MEDIUM DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*INGUINAL REGION	(24)	(24)	(24)	(24)
NECROSIS, FAT	2 (8%)	1 (4%)	8 (33%)	3 (13%)
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NONE				

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS FED DIELDRIN IN THE DIET

	CONTROL DOSE	LOW DOSE	MEDIUM DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	24	24	24	24
ANIMALS MISSING				1
ANIMALS NECROPSIED	24	24	24	23
ANIMALS EXAMINED HISTOPATHOLOGICALLY	24	24	24	23
INTEGUMENTARY SYSTEM				
*SKIN	(24)	(24)	(24)	(23)
EPIDERMAL INCLUSION CYST			1 (4%)	
*SUBCUT TISSUE	(24)	(24)	(24)	(23)
HEMORRHAGE				1 (4%)
ABSCESS, NOS			1 (4%)	
RESPIRATORY SYSTEM				
#TRACHEA	(21)			
INFLAMMATION, ACUTE	1 (5%)			
#LUNG/BRONCHUS	(23)	(24)	(24)	(23)
INFLAMMATION, NOS	1 (4%)	2 (8%)	1 (4%)	
#LUNG	(23)	(24)	(24)	(23)
ATELECTASIS	1 (4%)	1 (4%)	4 (17%)	3 (13%)
CONGESTION, NOS	10 (43%)	11 (46%)	14 (58%)	6 (26%)
EDEMA, NOS				1 (4%)
PETECHIA			1 (4%)	1 (4%)
INFLAMMATION, FOCAL	1 (4%)			
INFLAMMATION, INTERSTITIAL	1 (4%)			
ABSCESS, NOS	2 (9%)			
ADHESION, NOS			1 (4%)	
HEMATOPOIETIC SYSTEM				
#SPLEEN	(23)	(22)	(24)	(22)
CONGESTION, NOS				1 (5%)
REACTION, FOREIGN BODY	1 (4%)			2 (9%)
FIBROSIS	1 (4%)			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL DOSE	LOW DOSE	MEDIUM DOSE	HIGH DOSE
HEMATOPOIESIS		1 (5%)		
#LYMPH NODE	(3)	(1)	(2)	(2)
LYMPHANGIECTASIS				1 (50%)
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#LIVER	(24)	(24)	(24)	(23)
CONGESTION, NOS	3 (13%)	2 (8%)	1 (4%)	3 (13%)
INFLAMMATION, GRANULOMATOUS		1 (4%)	2 (8%)	
REACTION, FOREIGN BODY	2 (8%)			2 (9%)
NECROSIS, FOCAL			1 (4%)	
NECROSIS, ISCHEMIC	1 (4%)			
#STOMACH	(24)		(4)	(6)
DIVERTICULUM				1 (17%)
CONGESTION, NOS			1 (25%)	
INFLAMMATION, NOS			1 (25%)	
#DUODENUM	(3)			(1)
CONGESTION, NOS				1 (100%)
INFLAMMATION, NOS	1 (33%)			
URINARY SYSTEM				
#KIDNEY	(22)	(24)	(24)	(23)
CALCINOSIS, NOS		1 (4%)		
#URINARY BLADDER	(14)			
CALCULUS, NOS	1 (7%)			
ENDOCRINE SYSTEM				
#PITUITARY	(24)	(23)	(24)	(23)
CYST, NOS		1 (4%)		
CONGESTION, NOS	4 (17%)	2 (9%)	2 (8%)	6 (26%)
HEMORRHAGE		2 (9%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL DOSE	LOW DOSE	MEDIUM DOSE	HIGH DOSE
#ADRENAL			(2)	(1)
CONGESTION, NOS				1 (100%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(24)	(24)	(24)	(23)
HYPERPLASIA, NOS				1 (4%)
HYPERPLASIA, CYSTIC	1 (4%)			
*VAGINA	(24)	(24)	(24)	(23)
NECROSIS, FAT	1 (4%)			
#UTERUS	(22)	(10)	(8)	(13)
HYDROMETRA	2 (9%)	3 (30%)	1 (13%)	1 (8%)
CONGESTION, NOS				1 (8%)
PYOMETRA	5 (23%)	2 (20%)	4 (50%)	4 (31%)
ABSCESS, NOS	1 (5%)			1 (8%)
#UTERUS/ENDOMETRIUM	(22)	(10)	(8)	(13)
INFLAMMATION, NOS				1 (8%)
INFLAMMATION, FOCAL	1 (5%)			
HYPERPLASIA, NOS			1 (13%)	1 (8%)
HYPERPLASIA, CYSTIC	2 (9%)			
#OVARY	(21)	(3)		(1)
CYST, NOS	1 (5%)	1 (33%)		1 (100%)
ABSCESS, NOS	1 (5%)	3 (100%)		
CORPUS LUTEUM		1 (33%)		
NERVOUS SYSTEM				
#BRAIN/MENINGES	(24)	(24)	(23)	(23)
INFLAMMATION, NOS				1 (4%)
#BRAIN	(24)	(24)	(23)	(23)
CONGESTION, NOS		1 (4%)		
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL DOSE	LOW DOSE	MEDIUM DOSE	HIGH DOSE
BODY CAVITIES				
*INGUINAL REGION	(24)	(24)	(24)	(23)
NECROSIS, FAT	1 (4%)	1 (4%)	1 (4%)	
*PLEURA	(24)	(24)	(24)	(23)
INFLAMMATION, NOS			1 (4%)	
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED		2		1
ANIMAL MISSING/NO NECROPSY				1

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

APPENDIX C

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN RATS FED DIELDRIN IN THE DIET

Table C1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Dieldrin in the Diet[a]

Topography: Morphology	Matched Control	Low Dose	Mid Dose	High Dose
Hematopoietic System: Leukemia[b]	2/24 (8)	5/24 (21)	5/24 (21)	5/24 (21)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		2.500	2.500	2.500
Lower Limit		0.459	0.459	0.459
Upper Limit		24.045	24.045	24.045
Weeks to First Observed Tumor	83	74	86	80
Pituitary: Adenoma, NOS[b]	0/24 (0)	3/24 (13)	1/24 (4)	1/24 (4)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		Infinite	Infinite	Infinite
Lower Limit		0.622	0.055	0.055
Upper Limit		Infinite	Infinite	Infinite
Weeks to First Observed Tumor	--	85	97	100

Table C1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Dieldrin in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	Mid Dose	High Dose
Testis: Interstitial-cell Tumor[b]	24/24 (100)	23/24 (96)	24/24 (100)	20/24 (83)
P Values[c,d]	P = 0.009 (N)	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.958	--	0.833
Lower Limit		0.000	--	0.000
Upper Limit		1.043	--	1.200
Weeks to First Observed Tumor	83	74	86	62

[a]Treated groups received doses of 2, 10, or 50 ppm in feed.

[b]Number of tumor-bearing animals/number of animals necropsied (percent).

[c]Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when $P < 0.05$; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a treated group is the probability level for the Fisher exact test for the comparison of that treated group with the matched-control group when $P < 0.05$ for the control group; otherwise, not significant (N.S.) is indicated.

[d]A negative trend (N) indicates a lower incidence in a treated group than in the control group.

[e]The probability level for departure from linear trend is given when $P < 0.05$ for any comparison.

[f]The 95% confidence interval of the relative risk between each treated group and the matched-control group.

Table C2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Dieldrin in the Diet[a]

Topography: Morphology	Matched Control	Low Dose	Mid Dose	High Dose
Hematopoietic System: Leukemia[b]	1/24 (4)	3/24 (13)	5/24 (21)	5/23 (22)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		3.000	5.000	5.217
Lower Limit		0.265	0.622	0.652
Upper Limit		150.246	224.379	233.437
Weeks to First Observed Tumor	79	94	70	82
Pituitary: Adenoma, NOS[b]	2/24 (8)	7/24 (29)	4/24 (17)	2/23 (9)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		3.500	2.000	1.043
Lower Limit		0.759	0.321	0.081
Upper Limit		31.328	20.335	13.306
Weeks to First Observed Tumor	101	84	98	105

Table C2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Dieldrin in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	Mid Dose	High Dose
Uterus: Endometrial Stromal Polyp[b]	13/24 (54)	7/24 (29)	4/24 (17)	4/23 (18)
P Values[c,d]	P = 0.047 (N)	N.S.	P = 0.007 (N)	P = 0.009 (N)
Departure from Linear Trend[e]	P = 0.031			
Relative Risk (Matched Control)[f]		0.538	0.308	0.321
Lower Limit		0.231	0.089	0.094
Upper Limit		1.179	0.828	0.862
Weeks to First Observed Tumor	96	104	105	105
Uterus: Endometrial Stromal Sarcoma[b]	0/24 (0)	0/24 (0)	0/24 (0)	2/23 (9)
P Values[c,d]	P = 0.039	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		--	--	Infinite
Lower Limit		--	--	0.318
Upper Limit		--	--	Infinite
Weeks to First Observed Tumor	--	--	--	104

Table C2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Dieldrin in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	Mid Dose	High Dose
Uterus: Endometrial Stromal Polyp or Sarcoma[b]	13/24 (54)	7/24 (29)	4/24 (17)	6/23 (26)
P Values[c,d]	N.S.	N.S.	P = 0.007 (N)	P = 0.048 (N)
Departure from Linear Trend[e]	P = 0.026			
Relative Risk (Matched Control)[f]		0.539	0.308	0.482
Lower Limit		0.231	0.089	0.190
Upper Limit		1.179	0.828	1.106
Weeks to First Observed Tumor	96	104	105	104
Mammary Gland: Adenoma, NOS[b]	0/24 (0)	2/24 (8)	0/24 (0)	0/23 (0)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		Infinite	--	--
Lower Limit		0.305	--	--
Upper Limit		Infinite	--	--
Weeks to First Observed Tumor	--	104	--	--

Table C2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Dieldrin in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	Mid Dose	High Dose
Mammary Gland: Fibroadenoma[b]	2/24 (8)	0/24 (0)	0/24 (0)	2/23 (9)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.000	0.000	1.043
Lower Limit		0.000	0.000	0.081
Upper Limit		3.283	3.283	13.306
Weeks to First Observed Tumor	105	--	--	81

[a]Treated groups received doses of 2, 10, or 50 ppm in feed.

[b]Number of tumor-bearing animals/number of animals necropsied (percent).

[c]Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when $P < 0.05$; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a treated group is the probability level for the Fisher exact test for the comparison of that treated group with the matched-control group when $P < 0.05$ for the control group; otherwise, not significant (N.S.) is indicated.

[d]A negative trend (N) indicates a lower incidence in a treated group than in the control group.

[e]The probability level for departure from linear trend is given when $P < 0.05$ for any comparison.

[f]The 95% confidence interval of the relative risk between each treated group and the matched-control group.

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